



Chemistry, Manufacturing, & Controls (CMC) Requirements

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Outline

- General information and references
- CMC Expectations
 - Drug Substance
 - Drug Product
- Additional Considerations



References

- Content and format of an application – 21 CFR 314.50
- Guidances (including ICH):
 - <http://www.fda.gov/cder/guidance/index.htm>
- MaPPs: <http://www.fda.gov/cder/mapp.htm>
- GMPs:
<http://www.fda.gov/cder/regulatory/applications/compliance.htm>
- Additional helpful information:
<http://www.fda.gov/cder/regulatory/default.htm#Regulatory>



General

- ANDA/NDA Submission:
 - Format:
 - CTD recommended but not required
 - Can be either paper or electronic (eCTD)
 - Can reference required information in Drug Master File (DMF)
 - i.e., DMF reference for drug substance, packaging components, excipients
 - Must have appropriate Letter of Authorization (LOA) referencing the location(s) of the information in the DMF/NDA.
 - List of DMF holders: <http://www.fda.gov/cder/dmf/>
- For NDA, we recommend a pre-submission meeting



CMC Expectations

- Full description of the composition, manufacture, and specifications under 21 CFR 314.50(d)(1) and, for ANDAs, 21 CFR 314.94
- Must include Chemistry, Manufacturing, and Controls (CMC) info on:
 - Drug substance
 - Drug product and excipients
 - Packaging components
- Additional information as appropriate (e.g., comparison studies)



Drug Substance (DS)

Drug substance: An active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure or any function of the human body..." [21 CFR 314.3]



Drug Substance (DS)*

- Full description of the drug substance
 - Identity, physical, and chemical characteristics, and Stability
 - Method of synthesis (or isolation) and purification, including appropriate selection of starting materials
 - Manufacturing process controls (quality controls)
 - Specifications (including test methods) necessary to ensure purity and drug product performance
 - Level and qualification of impurities**
 - Container closure and stability information
- Name, address, & contact info of manufacturer
- May reference DMF, with appropriate LOA, for this information

*regulation citation: 21 CFR 314.50(d)(1)(ii)

**ICH guidance Q3a&c



Drug Substance

- Complexity may depend upon:
 - Sources and methods of preparation
 - Synthesis
 - Chemical, enzymatic
 - Single-step, multi-step, stereo-specific, etc.
 - Fermentation
 - Biotechnology – Recombinant, Transgenic, etc.
 - Naturally derived
 - Animal, botanical, mineral
 - BSE considerations if bovine derived
 - Isolation, extraction, purification, etc.
 - Physico-chemical and thermal stability



Drug Substance Stability

- Retest date or expiry assigned based upon data
- Stability testing protocol
 - Stability testing under controlled conditions
 - Accelerated 45°C/75% RH
 - Room Temperature (RT) 25°C/60% RH
 - Tests & acceptance criteria
 - Stability indicating assay
 - Testing frequency
 - ICH Q1A
- Container closure system representative of large bulk container/drum
- Submission expectations
 - For NDAs
 - 3 batches - 6 months RT and accelerated data
 - May statistically project expiry up to 6 months past RT data (trending!)
 - For ANDAs
 - 1 batch - 3 months accelerated
 - 3 months satisfactory accelerated data may permit 24 months expiry



Drug Product*

- The marketed dosage form designed to consistently deliver the drug substance at the desired rate
- Complexity may depend upon:
 - Physico-chemical, thermal stability of the formulation components
 - Route of administration
 - Onset of action
 - Site of action
 - Dosage form
 - Drug delivery system

*Regulation citation: 21 CFR 314.3(b)



Drug Product (DP)*

- Description & composition/formulation of the DP
 - A list of all components used in the manufacture of the DP, even if removed during manufacturing (e.g., solvents)
 - Composition of the drug product
 - Quantitative composition of drug product
 - List sub-formulations separately (e.g., tablet coating, mixture of IR and MR granules)
 - List tracers
 - Proprietary mixtures such as colors or flavors can be listed by their proprietary name (e.g., DMF)
 - Excipients on the “inactive ingredient list” for the amount and dosage form used do not need to be qualified

*Regulation citation: 21 CFR 314.50(d)(1)(ii)



Drug Product (cont.)

- Name, address, & contact info of the DP manufacturer(s)
- Description of the manufacturing & packaging processes, including process controls
- Container closure system
- Sterility assurance for sterile products
 - Guidance:
 - <http://www.fda.gov/cder/guidance/old031fn.pdf>
 - Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice
- Drug Delivery Systems, if appropriate
 - Modified release dosage forms
 - Transdermal patches
 - Oral inhalation drug products
- Environmental Assessment
 - *Regulation citations: 21 CFR 25.30, 25.31, & 25.40*
 - *Guidance for Industry for the submission of Environmental Assessment for Drug Applications and supplements (Nov. 1995)*



Drug Product Stability (shelf life)*

- To establish expiry based upon data
- Stability Protocol
 - Storage Conditions
 - Room temperature (RT) (25°C/60% relative humidity)
 - Accelerated (40°C/75% relative humidity)
 - Tests & acceptance criteria
 - Stability indicating assay
 - Testing frequency
 - ICH Q1A
- Submission expectations
 - For NDAs
 - 3 batches - 6 months RT and accelerated data
 - May statistically project expiry up to 6 months past RT data (trending!)
 - For ANDAs
 - 1 batch - 3 months accelerated
 - 3 months satisfactory accelerated data may permit 24 months expiry



Drug Product - Specifications

- Specifications are the quality standards (i.e., tests, analytical procedures, & acceptance criteria) provided in the application to ensure the quality and performance of the DS, DP, intermediates, raw materials, reagents, container closure systems, etc. in order to assure safety and efficacy
- Examples for solid oral dosage forms may include:
 - Appearance
 - Assay/potency
 - In-vitro dissolution or disintegration test
 - Impurity profile
 - Content uniformity
 - Other critical quality attributes, as appropriate
- USP monograph/public standards are considered minimum requirements
 - Additional specifications may be needed (e.g., impurities)



Additional considerations

- All facilities used in the manufacture of the drug (i.e., DS, DP, packagers, testers) should be ready for inspection upon submission of the application
- Facilities should operate under Current Good Manufacturing Practices (CGMPs)
 - CGMP Regulations 21 CFR 210 & 211
 - CGMP Guidances
<http://www.fda.gov/cder/guidance/index.htm#CGMPS-Eff>
 - Inspection will evaluate conformance to CGMPs



THANK YOU!

**For further information, contact ONDQA
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